CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040204

Trade Name: DICYCLOMINE HYDROCHLORIDE CAPSULES USP 10MG

Generic Name: Dicyclomine Hydrochloride Capsules USP 10mg

Sponsor : West-Ward Pharmaceutical Corp.

Approval Date: February 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040204

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EA/FONSI				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040204

APPROVAL LETTER

ANDA 40-204

West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Marro-Jelicks
465 Industrial Way West
Eatontown, NJ 07724

Dear Madam:

This is in reference to your abbreviated new drug application dated August 1, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dicyclomine Hydrochloride Capsules USP, 10 mg.

Reference is also made to your amendment dated January 24, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dicyclomine Hydrochloride Capsules USP, 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Bentyl® Capsules, 10 mg of Hoechst Marion Roussel Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 2/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040204

FINAL PRINTED LABELING

NDC 0143-3126-01

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each capsule contains:
Dicyclomine Hydrochloride, USP ..... 10 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

C-1

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3126-01 6

Exp. Date:

Control No.:

NDC 0143-3126-01

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Manufactured by:
West-ward Pharmaceutical Corp.
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Control No.:

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10 mg

CAUTION: Federal law prohibits dispensing without prescription.

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West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each capsule contains:
Dicyclomine Hydrochloride, USP ..... 10 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

C-1

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3126-01 6

Exp. Date:

Control No.:

NDC 0143-3126-10

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each capsule contains:
Dicyclomine Hydrochloride, USP ..... 10 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

M-1

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3126-10 8

Exp. Date:

Control No.:

NDC 0143-3126-10

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each capsule contains:
Dicyclomine Hydrochloride, USP ..... 10 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

M-1

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3126-10 8

Exp. Date:

Control No.:

NDC 0143-3126-10

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each capsule contains:
Dicyclomine Hydrochloride, USP ..... 10 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

M-1

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3126-10 8

Exp. Date:

Control No.:

NDC 0143-3126-10

Dicyclomine Hydrochloride Capsules, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Each capsule contains:
Dicyclomine Hydrochloride, USP 1

USUAL ADULT DOSAGE:
See accompanying product literatu for complete information.

M-1

re at controlled room temperature 5°-30°C (59°-86°F). Protect from light and moisture.

ispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

0143-3126-10 8

lo.:

Central Nervous System: dizziness, light-headedness, tingling, headache, drowsiness, weakness, nervousness, numbness, mental confusion and/or excitement (especially in elderly persons), dyskinesia, lethargy, syncope, speech disturbance, insomnia

Ophthalmologic: blurred vision, diplopia, mydriasis, cycloplegia, increased ocular tension

Dermatologic/Allergic: rash, urticaria, itching, and other dermal manifestations; severe allergic reaction or drug idiosyncrasies including anaphylaxis

Genitourinary: urinary hesitancy, urinary retention

Cardiovascular: tachycardia, palpitations

Respiratory: Dyspnea, apnea, asphyxia (see **WARNINGS**)

Other: decreased sweating, nasal stuffiness or congestion, sneezing, throat congestion, impotence, suppression of lactation (see **PRECAUTIONS: Nursing Mothers**)

DRUG ABUSE AND DEPENDENCE: Abuse of and/or dependence on dicyclomine for anticholinergic effects have been rarely reported.

OVERDOSAGE: Signs and Symptoms: The signs and symptoms of overdosage are headache; nausea; vomiting; blurred vision; dilated pupils; hot, dry skin; dizziness; dryness of the mouth; difficulty in swallowing; and CNS stimulation. A curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis).

Oral LD_{50}: The acute oral LD_{50} of the drug is 625 mg/kg in mice.

Minimum Human Lethal Dose/Maximum Human Dose Recorded: The amount of drug in a single dose that is ordinarily associated with symptoms of overdosage or that is likely to be life threatening, has not been defined. The maximum human oral dose recorded was 600 mg by mouth in a 10-month-old child and approximately 1500 mg in an adult, each of whom survived.

In three of the infants who died following administration of dicyclomine hydrochloride (see **WARNINGS**), the blood concentrations of drug were 200, 220, and 505 ng/mL, respectively.

Dialysis: It is not known if dicyclomine hydrochloride is dialyzable.

Treatment: Treatment should consist of gastric lavage, emetics, and activated charcoal. Sedatives (e.g., short-acting barbiturates, benzodiazepines) may be used for management of overt signs of excitement. If indicated, an appropriate parenteral cholinergic agent may be used as an antidote.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE ADJUSTED TO INDIVIDUAL PATIENT NEEDS. (See **CLINICAL PHARMACOLOGY.**)

Adults-Oral
The only oral dose clearly shown to be effective is 160 mg per day (in 4 equally divided doses). Since this dose is associated with a significant incidence of side effects, it is prudent to begin with 80 mg per day (in 4 equally divided doses). Depending upon the patient's response during the first week of therapy, the dose should be increased to 160 mg per day unless side effects limit dosage escalation.

If efficacy is not achieved within 2 weeks or side effects require doses below 80 mg per day, the drug should be discontinued. Documented safety data are not available for doses above 80 mg daily for periods longer than 2 weeks.

HOW SUPPLIED: Dicyclomine Hydrochloride Capsules USP, 10 mg are supplied as dark blue capsules printed "West-ward 3126" and are available in:

Bottles of 100 capsules.
Bottles of 1000 capsules.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724
Issued January 1997

DICYCLOMINE HYDROCHLORIDE CAPSULES, USP

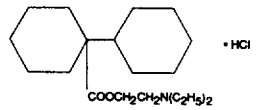
Issued 01/97

0 3126-0197-00 1

DESCRIPTION: Dicyclomine hydrochloride is an antispasmodic and anticholinergic (antimuscarinic) agent available in the following form:

Each capsule, for oral administration, contains 10 mg of dicyclomine hydrochloride. Each capsule also contains the following inactive ingredients: Corn Starch, Lactose Monohydrate, Magnesium Stearate, and Microcrystalline Cellulose. Capsule shells contain FD&C Blue No. 1, FD&C Red No. 4, and Gelatin. The imprinting ink contains Titanium Dioxide.

Chemically, dicyclomine hydrochloride is [bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethylester, hydrochloride with the structural formula:



Molecular Formula $C_{19}H_{35}NO_2 \cdot HCl$ M.W. 345.96

Dicyclomine hydrochloride occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether.

CLINICAL PHARMACOLOGY: Dicyclomine relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via a dual mechanism: (1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 the milligram potency of atropine (*in vitro*, guinea pig ileum); and (2) a direct effect upon smooth muscle (musculotropic) as evidenced by dicyclomine's antagonism of bradykinin- and histamine-induced spasms of the isolated guinea pig ileum. Atropine did not affect responses to these two agonists. *In vivo* studies in cats and dogs showed dicyclomine to be equally potent against acetylcholine (ACh)- or barium chloride ($BaCl_2$)-induced intestinal spasm while atropine was at least 200 times more potent against effects of ACh than $BaCl_2$. Tests for mydriatic effects in mice showed that dicyclomine was approximately 1/500 as potent as atropine; antisialagogue tests in rabbits showed dicyclomine to be 1/300 as potent as atropine.

In man, dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60-90 minutes. The principal route of elimination is via the urine (79.5% of the dose). Excretion also occurs in the feces, but to a lesser extent (8.4%). Mean half-life of plasma elimination in one study was determined to be approximately 1.8 hours when plasma concentrations were measured for 9 hours after a single dose. In subsequent studies, plasma concentrations were followed for up to 24 hours after a single dose, showing a secondary phase of elimination with a somewhat longer half-life. Mean volume of distribution for a 20 mg oral dose is approximately 3.65 L/kg suggesting extensive distribution in tissues.

In controlled clinical trials involving over 100 patients who received drug, 82% of patients treated for functional bowel/irritable bowel syndrome with dicyclomine hydrochloride at initial doses of 160 mg daily (40 mg q.i.d.) demonstrated a favorable clinical response compared with 55% treated with placebo. ($P<.05$). In these trials, most of the side effects were typically anticholinergic in nature (see table) and were reported by 61% of the patients.

Side Effect	Dicyclomine Hydrochloride (40 mg q.i.d.) %	Placebo %
Dry Mouth	33	5
Dizziness	29	2
Blurred Vision	27	2
Nausea	14	6
Light-Headedness	11	3
Drowsiness	9	1
Weakness	7	1
Nervousness	6	2

Nine percent (9%) of patients were discontinued from the drug because of one or more of these side effects (compared with 2% in the placebo group). In 41% of the patients with side effects, side effects disappeared or were tolerated at the 160 mg daily dose without reduction. A dose reduction from 160 mg daily to an average daily dose of 90 mg was required in 46% of the patients with side effects who then continued to experience a favorable clinical response; their side effects either disappeared or were tolerated. (See **ADVERSE REACTIONS**.)

INDICATIONS AND USAGE: For the treatment of functional bowel/irritable bowel syndrome.

CONTRAINDICATIONS:

1. Obstructive uropathy
2. Obstructive disease of the gastrointestinal tract
3. Severe ulcerative colitis (See **PRECAUTIONS**)
4. Reflux esophagitis
5. Unstable cardiovascular status in acute hemorrhage
6. Glaucoma
7. Myasthenia gravis
8. Evidence of prior hypersensitivity to dicyclomine hydrochloride or other ingredients of this formulation
9. Infants less than 6 months of age (See **WARNINGS** and **PRECAUTIONS: Information for Patients.**)
10. Nursing Mothers (See **WARNINGS** and **PRECAUTIONS: Information for Patients.**)

WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and supportive measures instituted.

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful.

Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect.

These CNS signs and symptoms usually resolve within 12 to 24 hours after discontinuation of the drug.

There are reports that administration of dicyclomine hydrochloride syrup to infants has been followed by serious respiratory symptoms (dyspnea, shortness of breath, breathlessness, respiratory collapse, apnea, asphyxia), seizures, syncope, pulse rate fluctuations, muscular hypotonia, and coma. Death has been reported. No causal relationship between these effects observed in infants and dicyclomine administration has been established. DICYCLOMINE IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE AND IN NURSING MOTHERS. (See **CONTRAINDICATIONS** and **PRECAUTIONS: Nursing Mothers** and **Pediatric Use**).

Safety and efficacy of dicyclomine hydrochloride in pediatric patients have not been established.

PRECAUTIONS: General: Use with caution in patients with:

1. Autonomic neuropathy
2. Hepatic or renal disease
3. Ulcerative colitis - large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon (see **CONTRAINDICATIONS**)
4. Hyperthyroidism
5. Hypertension
6. Coronary heart disease
7. Congestive heart failure
8. Cardiac tachyarrhythmia
9. Hiatal hernia (see **CONTRAINDICATIONS**: reflux esophagitis)
10. Known or suspected prostatic hypertrophy.

Investigate any tachycardia before administration of dicyclomine hydrochloride, since it may increase the heart rate.

With overdosage, a curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis).

Information for Patients: Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug.

Dicyclomine is contraindicated in infants less than 6 months of age and in nursing mothers. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS: Nursing Mothers and Pediatric Use.**)

In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and a physician contacted.

Drug Interactions: The following agents may increase certain actions or side effects of anticholinergic drugs: amantadine, antiarrhythmic agents of class 1 (e.g., quinidine), antihistamines, antipsychotic agents (e.g., phenothiazines), benzodiazepines, MAO inhibitors, narcotic analgesics (e.g., meperidine), nitrates and nitrites, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity.

Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when taken concurrently with agents such as corticosteroids. (See also **CONTRAINDICATIONS.**)

Anticholinergic agents may affect gastrointestinal absorption of various drugs, such as slowly dissolving dosage forms of digoxin; increased serum digoxin concentrations may result. Anticholinergic drugs may antagonize the effects of drugs that alter gastrointestinal motility, such as metoclopramide. Because antacids may interfere with the absorption of anticholinergic agents, simultaneous use of these drugs should be avoided.

The inhibiting effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no known human data on long-term potential for carcinogenicity or mutagenicity.

Long-term studies in animals to determine carcinogenic potential are not known to have been conducted.

In studies in rats at doses of up to 100 mg/kg/day, dicyclomine hydrochloride produced no deleterious effects on breeding, conception, or parturition.

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Epidemiologic studies in pregnant women with products containing dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/day). Because animal reproduction studies are not always predictive of human response, dicyclomine hydrochloride as indicated for functional bowel/irritable bowel syndrome should be used during pregnancy only if clearly needed.

Nursing Mothers: Since dicyclomine hydrochloride has been reported to be excreted in human milk, DICYCLOMINE HYDROCHLORIDE IS CONTRAINDICATED IN NURSING MOTHERS. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Pediatric Use** and **ADVERSE REACTIONS.**)

Pediatric Use: (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS: Nursing Mothers.**) DICYCLOMINE HYDROCHLORIDE IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE.

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Controlled clinical trials have provided frequency information for reported adverse effects of dicyclomine hydrochloride listed in a decreasing order of frequency. (See **CLINICAL PHARMACOLOGY.**)

Not all of the following adverse reactions have been reported with dicyclomine hydrochloride. Adverse reactions are included here that have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action.

Gastrointestinal: dry mouth, nausea, vomiting, constipation, bloated feeling, abdominal pain, taste loss, anorexia

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040204

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO: 2

2. ANDA # 40-204

3. NAME AND ADDRESS OF APPLICANT
West-ward Pharmaceuticals Corp.
Attention: Ms. Elizabeth A. Marro-Jelicks
465 Industrial Way West
Eatontown, NJ 07724

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies, that to the best of their knowledge there are no patents referenced in the "orange book", 15th Edition. Also, no exclusivity exists for the listed drug Bentyl® manufactured by Merrel Dow.

6. PROPRIETARY NAME
Bentyl®

7. NONPROPRIETARY NAME
Dicyclomine Hydrochloride Capsules, USP

8. SUPPLEMENTS PROVIDED FOR
N/A

9. AMENDMENTS AND OTHER DATES
August 1, 1996 -- Original Submission
September 13, 1996 -- Acknowledgment letter (FDA)
November 8, 1996 -- Bio amendment
January 3, 1997 -- Bio Waiver granted
January 10, 1997 -- Chemistry & labeling deficiency minor facsimile issued
January 24, 1997 -- Response to FDA's deficiency by firm

10. PHARMACOLOGICAL CATEGORY
Treatment for irritable bowel syndrome

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(S)

(b)4 - Confidential Business

13. DOSAGE FORM
Capsules

14. POTENCY
10 mg

15. CHEMICAL NAME AND STRUCTURE
[Bicyclohexyl]-1-carboxylic acid, 2-(diethylamino)ethyl ester, hydrochloride.

$C_{19}H_{35}NO_2.HCl$; M.W. = 345.95.

16. RECORDS AND REPORTS
N/A

17. COMMENT
All the identified deficiencies have been corrected.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval of ANDA.

19. REVIEWER: DATE COMPLETED:

Radhika Rajagopalan, Ph.D. February 11, 1997

/S/ 2/25/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040204

BIOEQUIVALENCE REVIEW(S)

ANDA 40-204

JAN - 3 1997

West-ward Pharmaceuticals Corp.
Attention: Elizabeth A. Marro-Jelicks
465 Industrial Way West
Eatontown NJ 07724

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Dicyclomine HCl Capsules USP, 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

3. (b)4 - Confidential Business

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 1 6 1996

Dicyclomine
10 mg Capsule
ANDA # 40204
Reviewer: Andre J. Jackson
WP #40204SDW.896

West-Ward Pharmaceutical
Eatontown, New Jersey
Submission Dated:
August 1, 1996

Review of Fasting 10 mg
Bioequivalence Study and Dissolution Data
and Waiver Request

Background:

Dicyclomine is an antispasmodic and anticholinergic agent. The drug relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via a dual mechanism: (1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 the milligram potency of atropine (in vitro, guinea pig ileum); and (2) a direct effect upon smooth muscle (musculotropic) as evidenced by dicyclomine's antagonism of bradykinin and histamine induce spasma in the guinea pig ileum.

In man, dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60-90 minutes. The principal route of elimination is via the urine (79.5% of the dose). Excretion also occurs in the feces, but to a lesser extent(8.4%). Mean half-life of plasma elimination in one study was determined to be approximately 1.8 hours when plasma concentrations were measured for 9 hours after a single dose. In subsequent studies, plasma concentrations were followed up to 24 hours after a single dose, showing a secondary phase of elimination with a somewhat longer half-life. Mean volume of distribution for a 20 mg oral dose is approximately 3.65 L/kg suggesting extensive distribution in tissues.

The reference listed drug is Bentyl® manufactured by Marion Merrell Dow.

Methods:

(b)4 - Confidential Business

conducted on May 8,1996 while period II samples were collected on May 15, 1996.

Characterization of Study Group:

SUBJECT SELECTION

Subjects

This study involved healthy male volunteers, 18-45 years of age, weighing at least 60 kg, who are within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983).

Screening

Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits were recorded. Each subject received a complete physical examination, 12-lead EKG and the laboratory tests of hematologic, hepatic and renal functions listed below. Only medically healthy subjects with clinically normal laboratory profiles and EKGs were enrolled in the study.

Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen.

Exclusions

History or presence of significant:

- cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.

In addition, history or presence of:

- hypersensitivity or idiosyncratic reaction to dicyclomine HCl or any other anticholinergic/ antispasmodic agent;

- alcoholism or drug abuse.

Subjects who have been on an abnormal diet (for whatever reason) during the four weeks preceding the study.

Subjects who, through completion of this study, would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in one year.

Subjects who have participated in another clinical trial within 28 days of study start.

Prohibitions

No subject was permitted to take medication (including over-the-counter products) for the 7 days preceding the study. This prohibition did not include vitamins taken as nutritional supplements in non-therapeutic doses, as judged by the attending physician.

The consumption of alcohol- or xanthine-containing beverages and foods was prohibited for 24 hours before dosing and throughout the period of sample collection.

If drug therapy other than that specified in the protocol was required during the time of sample collection, or during the washout period between drug administrations, a decision to continue or discontinue the subject was made, based on the time the medication was administered and its pharmacology and pharmacokinetics.

CLINICAL PROCEDURES

Drug Administration

After a supervised overnight fast, subjects received an oral dose of the assigned formulation, with 240 mL of water at ambient temperature, according to a randomization scheme generated at Phoenix International Life Sciences.

Blood Sampling

Due to the sensitivity of dicyclomine to ultraviolet (UV) light, samples were collected and processed under conditions which minimized their UV exposure.

Blood samples were collected at the times specified under STUDY DESIGN, cooled in an ice bath and centrifuged under refrigeration as soon as possible. Pre-dose plasma samples were divided into 4 portions. All other plasma samples were divided into 2 portions. All samples were stored in suitably labelled tubes at -12°C or lower, pending assay. The location of venipuncture was varied from one draw to the next in order to minimize subject discomfort.

Activity

Subjects engaged in normal activity for the first 4 hours after drug administration, avoiding both vigorous exertion and complete rest. Subjects were cautioned against activities requiring mental alertness, judgment and physical coordination such as driving or operating machinery for a period of 24 hours after drug administration.

Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

Study Conduct

The study was done in 26 healthy males. Subjects 25 and 26 were designated as alternates. Subject 3 elected to withdraw from the study so the data from subjects 1,2 and 4-25 were analyzed.

A. Subjects fasted overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter. Standard meals were provided at 4 and approximately 9 hours after dosing.

B. The products employed in the study were:

1. Test: West-Ward Pharmaceuticals 10 mg dicyclomine capsule, Lot# 54175, potency 102%, Lot size [redacted](b)4 -[redacted]

2. Reference product: Merrell Dow 10 mg Bentyl® capsule Lot # 3656DB, expiration date 1/99, potency 97.1%.

There was a 7 day washout between doses.

C. 20 mg dose (2 x 10 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 25 subjects

Sequence	SUBJECT
A,B	3,4,5,8,9,10,12,14,15,17,19,20,25
B,A	1,2,6,7,11,13,16,18,21,22,23,24

Treatment A: West-Ward 2x10 mg dicyclomine capsule

Treatment B: Merrell Dow 2x10 mg Bentyl® capsule

The formulation for the 10 mg capsule is given in table 2.

Table 2. COMPOSITION OF THE 10 MG Dicyclomine Capsule

INGREDIENTS	MG/UNIT
Dicyclomine, USP	10.2
Microcrystalline Cellulose, NF	(b)4 - Confidential Business
Corn Starch Purity 21, NF	
Lactose Monohydrate,NF	
Magnesium Stearate, NF	
Total Fill Weight	185.0*

*Includes 2% excess.

D. Plasma was collected pre-dose and at the following times post-dose: 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8 10, 12, 16 and 24 hours after dosing.

E. During the study subjects were monitored for adverse reactions. In addition sitting blood pressure and heart rate were performed before dosing and at approximately 1, 2, 3 and 4 hours after dosing.

III. **Analytical**

Samples for this study were analyzed from May 21, 1996 to June 5, 1996. The assay used (b)4 - Confidential

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

RESULTS

Table 3.Dicyclomine plasma levels, Mean(± SD), for the subjects N=24 that received the test and reference formulations (2x10 mg capsules) after an overnight fast. Concentrations are ng/ml.

Time hrs	West-Ward Test		Merrell-Dow Reference	
	Mean	SD	Mean	SD
0	0	0	0	0
0.33	4.46	12.34	3.15	4.23
0.67	41.99	27.69	38.00	20.97
1	57.59	22.72	57.74	22.15
1.5	53.23	17.10	54.31	21.63
2	43.78	12.20	44.04	21.75
3	26.83	8.22	28.80	14.03
4	18.71	6.41	19.93	9.88
6	8.14	2.84	8.49	4.66
8	4.77	1.74	5.04	2.98
10	3.40	1.24	3.53	2.05
12	2.54	1.03	2.58	1.58
16	1.72	0.90	1.86	1.37
24	1.07	0.97	1.23	1.19

Table 4. Mean pharmacokinetic parameters ±% CV for subjects that received the test and reference dicyclomine formulations following an overnight fast.

TREATMENT				
Variable	A=Test	B=Reference	Ratio (A/B)%	N
AUCL[2] (ng/mlxhr)	207.1±34.4	213.2±47.2		24
LNAUCL[4]	194.6	193.64	99.9	24
AUCI[3] (ng/mlxhr)	221.8±36.4	236.6±54.0		23
LNAUCI[4]	207.26	210.48	98.4	23
Cmax(ng/ml)	61.59±36.9	61.78±37.3		24
LNCmax[4]	57.60	57.81	99.1	24
KEL-1 (hr)	0.11	0.11		
HALF (hr)	7.62	8.75		
Tmax (hr)	1.21	1.24		

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 -infinity)
[4]Log Transformed(LNAUCL,LNAUCI,LNCmax) -Ratio is Geometric Mean expressed as a per cent-Antilog of the mean is reported

Table 5. Mean pharmacokinetic parameters ± SD for subjects that received the test and reference dicyclomine formulations following an overnight fast. These parameters reflect the deletion of subjects 24 and 25 whose values were determined from a calibration curve that did not meet SOP.

TREATMENT				
Variable	A=Test	B=Reference	Ratio (A/B)%	N
AUCL[2] (ng/mlxhr)	197.4±64.2	207.1±102.2		22
LNAUCL[4]	186.5	187.5	99.5	22
AUCI[3] (ng/mlxhr)	213.3±71.0	231.7±128.7		22
LNAUCI[4]	200.98	205.73	97.7	22
Cmax(ng/ml)	59.77±22.47	60.54±23.44		22
LNCmax[4]	55.88	56.49	98.9	22

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 -infinity)
[4]Log Transformed(LNAUCL,LNAUCI,LNCmax) -Ratio is Geometric Mean expressed as a per cent-Antilog of the mean is reported

CONFIDENCE INTERVALS WERE CALCULATED BY REVIEWER

Table 6. 90% Confidence Intervals for dicyclomine based on Ln transformed data n=22.

Ln AUC(0-t)	(88 112)
Ln AUC(0-INF)	(86 110)
Ln Cmax	(90 109)

Adverse Effects

There were few reported adverse effects and they are presented in appended Table 7 and were associated with the reference product.

Subject Drop-outs

There was one subject #3 that dropped out of the study. The two extra subjects were designated as alternates and # 25 was used to replace #3.

Sample Repeats

There were 3 sample repeats out of 672 samples analyzed(0.4%). The major reason was that the original sample was anomalous sample value.

Dissolution (Note:USP method and Specification)

The dissolution study for diclocyclomine was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	500 ml 0.01N HCL
No. of Units Analyzed:	12
Specifications:	NLT [redacted](h)4 in 45 min
Assay:	[redacted](h)4 - [redacted]

Comments:

1. The 90% confidence intervals for the fasting study are within the acceptable range of 80-125% of the reference.

2. [redacted]

3. (b)4 - Confidential Business

Recommendation:

1. The bioequivalence study conducted by West-Ward Pharmaceuticals on its 10 mg dicyclomine HCL capsule Lot # 54175 comparing it to Marion Merrell Dow's 10 mg Bentyl® capsule Lot # 3656DB has been found to be acceptable by the Division of Bioequivalence. Therefore West-Ward's 10 mg dicyclomine capsule is deemed bioequivalent to Bentyl® 10 mg capsule manufactured by Marion Merrell Dow.

2. The in vitro dissolution testing conducted on lot # 54175 of the dicyclomine 10 mg capsule is acceptable.

3. The dissolution testing conducted by West-Ward on its 10 mg strength capsule,Lot No. 54031 is acceptable. Therefore, the 10 mg dicyclomine capsule manufactured from the alternate source is deemed bioequivalent to Bentyl® 10 mg capsule manufactured by Marion Merrell Dow.

4. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of 0.01N HCL at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

5. The firm should receive recommendations and comments 1-3.

Andre Jackson, Ph.D. /S/
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ Date: 12/11/96

Concur: /S/ Date: 12/16/96

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

ANDA# 40-204 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

Table 8 . In Vitro Dissolution Testing

Drug (Generic Name):Dicyclomine Hydrochloride
Dose Strength:10 mg Capsule
ANDA No.:40-204
Firm:West-Ward
Submission Date:August 1, 1996
File Name:40204SDW.896

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium: 0.01N HCL
Volume:500 ml
Specifications: NLT (b)4 in 45 min

Reference Drug: Bentyl
Assay Methodology: (b)4 - Confidential

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 54175 Strength(mg) 10			Reference Product Lot # 3656DB Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%C
15	95.1	(b)4 - Confidential Business	7.0	100.3	(b)4 - Confidential Business	4.8
30	103.6		1.9	100.7		4.4
45	104.5		1.6	100.4		5.1
60	105.2		1.5	101.3		4.9

Sampling Times (Minutes)	Test Product Lot # 54031-Alternate Source Strength(mg) 10		
	Mean	Range	%CV
15	89.6	(b)4 - Confidential Business	5.2
30	94.3		3.7
45	94.2		2.7
60	95.9		2.5

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu-tion	Inten-sity	Action/Comment
Product Code B														
2	1	07:02am 08/MAY/96	**Headache**											
			1.1d	11.0h	NS	D	PO	E	M	None	1.6d	R	N/A	None
21	1	07:40am 08/MAY/96	**Headache**											
			21.6h	30.0m	NS	D	PO	SP	M	None	22.1h	R	N/A	None
22	1	07:42am 08/MAY/96	**Dry throat**											
			5.6h	21.8h	NS	D	PO	SP	M	None	6.1h	N/A	N/A	Temperature: 36.8°C
											12.0h	U	M	Oral temperature: 37.1°C
											16.1h	U	M	Oral temperature: 37.5°C
											1.0d	D	M	None
											1.1d	R	N/A	None
22	1	07:42am 08/MAY/96	**Headache**											
			11.1h	17.3h	NS	D	PO	SP	M	None	12.0h	N/A	N/A	Oral temperature: 37.1°C
											1.0d	U	M	None
											1.2d	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = West-Ward 2 x 10 mg dicyclomine HCl capsules
B = Marion Merrell Dow (Bentyl) 2 x 10 mg dicyclomine HCl capsules

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MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up: Time after dosing	Evolu-tion	Inten-sity	Action/Comment
Product Code B															
22	1	07:42am 08/MAY/96	**Abdominal pain**	11.8h	16.5h	NS	D	PO	SP	M	None	1.0d	D	M	None
												1.2d	R	N/A	None
22	1	07:42am 08/MAY/96	**Feels pain at the back of the jaw when he swallows**	13.3h	15.0h	NS	D Dysphagia	PO	SP	M	None	1.0d	D	M	None
												1.2d	R	N/A	None

TIME UNITS: d=Days, h=Hours, m=Minutes
FORMS USED: PO=Physician Obs, AC=Addit. Comment, MP=Med.Prescrip.
SERIOUSNESS: S=Serious, NS=Non-Serious
CAUSALITY: D=Drug, P=Procedure, O=Other
PROBABILITY: D=Definite, PR=Probable, PO=Possible, U=Unlikely
REPORT METHOD: E=Elicited, SP=Spontaneous, O=Observed
INTENSITY: M=Mild, MO=Moderate, S=Severe
EVOLUTION: I=Increased, U=Unchanged, D=Decreased, R=Resolved
GENERAL: N/A = Not Applicable, N/R = Not Recorded

A = West-Ward 2 x 10 mg dicyclomine HCl capsules
B = Marion Merrell Dow (Bentyl) 2 x 10 mg dicyclomine HCl capsules

(b)4 - Confidential Business